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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/768,020 | 01/23/2001 | Ralph J. Greenspan | P-NI 4577 | 9299 |

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| EXAMINER | |
|---|---|
| PARAS JR, PETER | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 17 |

DATE MAILED: 10/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/768,020 | GREENSPAN ET AL. | |
| | Examiner | Art Unit | |
| | Peter Paras, Jr. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *1-21 and 30-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14,16,16*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152) PTO/2/23/03
6) ☐ Other: .

Applicant's amendments received on 3/6/03 and 6/30/03 have been entered. Claims 1-37 are pending. Claims 22-29 are under current consideration.

### *Election/Restrictions*

Claims 22-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

### *Priority*

The priority claim of the instant application has been perfected in view of the amendment to the first line of the specification filed on 3/6/03.

### *Drawings*

The corrected drawings filed on 3/6/03 have been approved.

### *Specification*

The previous objections to the specification have been withdrawn in view of the amendments to the specification.

Upon further consideration the previous written description rejection has been withdrawn and replaced by the written description as set forth below:

***Claim Rejections - 35 USC § 112, 1st paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The parent strains within the genus embraced by the claims have not been disclosed. Based upon the prior art there is expected to be variation among the species of parent strains, because the structures of parent strains would be expected to vary among individuals. The specification discloses mutant *Drosophila melanogaster* lacking the Appl gene (hereafter referred to as Appl$^{d}$) and does not disclose other parent strains embraced by the claims. There is no evidence on the record of a relationship between the structure of any parent strain embraced by the claims and Appl$^{d}$ that would provide any reliable information about the structure of other parent strains within the genus. There is no evidence on the record that Appl$^{d}$ had a known structural relationship to any other parent strain; the specification discloses only parent strain Appl$^{d}$; the art indicated

that there is variation between the structures of organisms that are parent strains. There is no evidence of record that would indicate that any of the parent strains embraced by the claims, when mated, would produce progeny with an altered phenotype that when modulated, by an agent when practicing the claimed invention, is correlative to treatment of Alzheimer's disease.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998).

In the instant case the claimed embodiments of parent strains, other than Appl$^{d}$, lack a written description. The specification fails to describe what strains fall into this genus and it was unknown as of Applicant's effective filing date that any of the parent strains embraced by the claims, when mated, would produce progeny with an altered phenotype that when modulated, by an agent when practicing the claimed invention, is correlative to treatment of Alzheimer's disease. The skilled artisan cannot envision the detailed chemical structure of the embraced parent strains, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of creating. Adequate written description requires more than a

mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only Appl[d].

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because Appl[d] is not representative of the claimed genus. Consequently, since Applicant was in possession of only Appl[d] and since the art recognized variation among the species of the genus of organisms that are parent strains, Appl[d] was not representative of the claimed genus. Therefore, Applicant was not in possession of the genus of parent strains as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claims 22-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of identifying a therapeutic agent for treating Alzheimer's disease comprising mating different parent strains to produce progeny and administering the agent to the progeny, wherein alteration of the phenotype of the progeny indicates that the agent can treat Alzheimer's disease.

The specification discusses that the invention features methods for mapping a network of functional gene interactions relating to Alzheimer's disease. See page 4 and throughout the specification. The specification discusses that the invention features a strain of Drosophila melanogaster lacking the Appl gene (hereafter referred to as $Appl^{d}$) and goes on to discuss methods of using $Appl^{d}$ as a parent strain for identifying therapeutic agents for treating Alzheimer's disease. See pages 5-6. While the specification provides extensive teachings pertaining to $Appl^{d}$, which exhibits a phenotype of defective phototaxis, the specification fails to provide any relevant teachings or specific guidance with regard to the progeny and their respective phenotypes obtained from crossing $Appl^{d}$ with a different Drosophila parent strain, in particular progeny that exhibit a phenotype that correlates to Alzheimer's disease, wherein when the phenotype is modulated by a candidate agent, said agent is capable of treating Alzheimer's disease (as is consistent with the discussion of the specification). Furthermore, the specification fails to even describe any particular type of phenotype exhibited by the progeny embraced by the claims and how such a phenotype may relate to Alzheimer's disease; the specification only asserts that the progeny would be useful

for identifying agent that can treat Alzheimer's disease. Given the lack of guidance provided by the specification it would have required undue experimentation to make and use the invention as claimed.

As a first issue, the claims when broadly interpreted read on transgenic organisms of all species. The specification has not provided guidance for creating transgenic organisms, in particular those whose genomes comprise mutated Alzheimer's disease genes or those that comprise any genetic variation, that can be used as parent strains when practicing the claimed invention. The specification has only taught the $Appl^{d}$ strain of *D. melanogaster*, which appears to be non-transgenic. As the specification fails to provide any relevant teachings or guidance with regard to the production of a transgenic organism as embraced by the claims, one of skill would not be able to rely on the state of the transgenic art for an attempt to produce transgenic organisms that could serve as parent strains for practicing the invention as claimed. This is because the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic organisms comprising a transgene of interest; it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration

into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); *e.g.*, specific promoters, presence or absence of introns, *etc.* As such guidance is lacking in the instant specification for the production of transgenic organisms that can be mated to produce progeny that can be used for identifying agents for treating Alzheimer's disease.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic organisms is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. See also Ebert et al. (Molecular Endocrinology, 1988). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who

report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 62, first paragraph. Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of even one transgenic organism whose genome comprises a mutation in an Alzheimer's disease gene or any genetic variation, it would have required undue experimentation to predict the results achieved in any one host organism, and therefore, the resulting phenotype.

As a second issue, the claims read on use of non-transgenic organisms of all species. The specification has provided guidance for use of the mutant D. melanogaster strain, $Appl^d$ as a first parent strain. However, the specification has not provided guidance for use of the other parent strains embraced by the claims. Furthermore, the instant specification has not taught which other strains could be used

as either first or second parent strains. Further, all the working examples provided by the instant specification are directed to $Appl^d$. However, if $Appl^d$ was used as the first strain, the specification has not provided guidance for selecting a second parent strain, which when mated with $Appl^d$ would produce progeny having a phenotype correlating to Alzheimer's disease, wherein the phenotype of the progeny is modulated by an agent that can treat Alzheimer's disease. As such it appears that the instant specification fails to support the breadth of the claims directed to all organisms that can be used as parent strains.

With regard to the phenotype of the progeny of the first and second strains, the specification has failed to teach any phenotype that correlates to Alzheimer's disease. Given the teachings of the specification and the plain language of the claims it appears that the phenotype of the progeny correlates to Alzheimer's disease. It is reasonable to make such an interpretation, as the claims require that an agent, which modulates a phenotype of the progeny, can treat Alzheimer's disease. The specification has taught that the $Appl^d$ flies have a phenotype of defective phototaxis. The specification however, has not provided guidance that correlates defective phototaxis or any phenotype, produced by mating $Appl^d$ with other strains of *Drosophila*, with Alzheimer's disease. The state of the prior art suggests that differences exist between Appl and APP such that one of skill would not expect a correlation between any phenotype exhibited by the progeny embraced by the claims and Alzheimer's disease. Luo et al (J. Neurosci., 1990, 10(12) : 3849-3861) teach isolation and characterization of APPL. Luo et al report differences in structure and expression between APPL and APP. For

example, on page 3849 Luo discusses that APPL lacks primary sequence homology with APP in the transmembrane domain or in the extracellular domain near the membrane-spanning region and suggests the β-amyloid sequence, which spans the border of extracellular and transmembrane domains of APP, is not found in APPL; the presence of β-amyloid peptide characterizes plaques found in Alzheimer's patients. With regard to expression of APPL as compared to APP, Luo et al suggest that APPL is expressed as only a single-size transcript in a neural-specific manner while APP "is expressed in many tissues and encodes a family of proteins consisting of several isoforms, some of which contain an additional protease inhibitor domain." See page 3849. It appears given the teachings of Luo et al that the structure, regulation, and function of APPL and APP are different. In light of such, it does not appear that a correlation exists between a phenotype exhibited by an $Appl^d$ fly or any progeny embraced by the claims and Alzheimer's disease. Moreover, Fossgreen et al (PNAS, 1998, 95: 13703-13708) teach that expression of human APP in transgenic *Drosophila* results in a blistered wing phenotype but does not result in the production of βA4 (the 4kDa peptide fragment in amyloid plaques and vascular deposits). The art of record however, is silent as to how a blistered wing phenotype correlates to Alzheimer's disease. Fossgreen et al goes on to suggest that despite the availability of APPL-deficient flies, APP-null mutants or transgenic mice expressing human APP, the physiological role of APP remains obscure. Given the teachings of the prior art it does not appear that a correlation exists between a phenotype exhibited by $Appl^d$ or any progeny embraced by the claims and Alzheimer's such that modulation of said

phenotype by an agent suggests that the agent is capable of treating Alzheimer's disease. With regard to the candidate agents embraced by the claims, the specification has not provided guidance for selecting any candidate agents to be used in the claimed methods. As such the skilled artisan would not know how to select agents, on the basis of their characteristics, for use in the claimed methods. Given the lack of guidance provided by the instant specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of parent strains of organisms other than $Appl^d$, the lack of direction or guidance provided by the specification for the production of parent strains of organisms other than $Appl^d$, the absence of working examples for the demonstration or correlation of phenotypes exhibited by $Appl^d$ flies or progeny thereof with Alzheimer's disease, the unpredictable state of the art with respect to transgene behavior in transgenic organisms, and the breadth of the claim drawn to any organism that can be used as a parent strain in the claimed methods, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

## Conclusion

**No claim is allowed.**

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER